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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/737,633	11/15/1996	FABRIZIO SAMARITANI	P/42-60	5401

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EXAMINER	
LANDSMAN, ROBERT S	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 09/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/737,633	Applicant(s) SAMARITANI ET AL.	
	Examiner Robert Landsman	Art Unit 1647	

-- Th MAILING DATE of this communication appears on the cover sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/23/02 .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1 and 3-10 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1, 3-7, 9 and 10 is/are rejected.

7)☒ Claim(s) 8 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

In view of the Board's direction given in the Remand mailed 5/23/02, the finality of the Office Action dated 3/7/00 has been withdrawn and prosecution on the merits is reopened in order to make the revised rejections.

1. Formal Matters

A. Claims 1 and 3-10 are pending in the application and are the subject of this Office Action.

B. All Statutes under 35 USC not found in this Action can be found, cited in full, in a previous Office Action.

2. Claim Objections

A. Claim 8 is objected to since it depends from rejected claim 1. However, this claim would be allowable if rewritten in independent format to include all of the limitations of the claim from which it depends.

3. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1, 3, 7, 9 and 10 are rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. (U.S. Patent No. 5,643,566) in view of Hershenson et al. (U.S. Patent No. 5,004,605). The claims recite a liquid pharmaceutical formulation consisting of about 0.6 to 24 MIU/ml of interferon-beta, mannitol, a buffer at a pH between 3.0 and 4.0 and, optionally, albumin. Furthermore, the interferon-beta can be recombinant and the albumin can be human albumin. The present invention also recites a process for the preparation of said pharmaceutical formulation and a hermetically sealed container comprising the said formulation. With regard to claim 1, both Hanisch et al (column 2) and Hershenson et al. (column 1) teach that stabilized formulations can contain recombinant IFN-beta. With regard to claim 7, both Hanisch et al. (column 9, line 32) and Hershenson et al. (column 3, line 29) teach that albumin can be used to stabilize IFN-beta. Specifically, Hanisch describes formulations for the stable storage of

"lipophilic proteins," including the particularly exemplified IL-2 and INF-beta (Abstract). It teaches that a formulation having essentially only INF-beta, human serum albumin and a buffer (as is obtained following practice of the prescribed purification protocol) may be prepared at an acidic pH, preferably 3.5, and that under such conditions "[t]he beta-INF formulation will remain stable and soluble." (Column 12, lines 53-65). It further teaches that the formulation "can be maintained as a liquid with or without a carbohydrate stabilizer," and that, following the optional addition of such stabilizer, the formulation may be lyophilized. Id. The patent teaches that a number of carbohydrate stabilizers, including mannitol, may be employed in the formulation it describes (column 9, lines 21-37). Since Hanisch et al. also teach that a therapeutically effective amount of INF-beta (column 5, line 27) can be used, for example, as an antiviral agent (column 2, line 34), the formulation of Hanisch et al. would suggest using any known dosage quantity of IFN-beta for that purpose.

Hanisch et al. also teach that lipophilic proteins such as IFN, are stable and soluble at a pH range of 3-4 and that low pH formulations can be either maintained as a liquid , or a carbohydrate stabilizer such as mannitol can be added. Hanisch et al. also teach pharmaceutical compositions comprising a therapeutically effective amount of a biologically active recominant lipophilic protein dissolved in a non-toxic, inert, therapeutically compatible aqueous based carrier medium at a pH at about 3-4 (column 5, lines 6-31). Hanisch et al. also teach process steps for the preparation of these pharmaceutical compositions (column 11, line 56 – column 12, line 46) and a sterile container (column 22, lines 53-57). Hanisch et al. do not exemplify a formulation consisting of about 0.6 – 24 MIU/ml of INF-beta. However, Hershenson et al. do teach using therapeutically effective amounts of IFN-beta (column 4, lines 42-43) in stabilized formulations, which INF-beta is also intended to be used as, for example, an antiviral agent (column 1, line 56), and that:

> the concentration of the stabilizer/solubilizers of this invention varies with the concentration of IFN-β in the formulation. For example, a high dosage formulation of IFN-β is that which contains about 1 to about 2 mg/ml of IFN-β in the final container vial (2 to 4 x 10^8 units per mg). A normal dosage formulation has about 0.25 mg/ml of IFN-β in the final container vial (0.5 x 10^8 units per mg); whereas, a low dosage formulation has about 0.125 mg/ml of IFN-β in the final container vial (0.25 x 10^8 units per mg). Generally lower dosage formulations of IFN-β require lower concentration ranges of the stabilizer/solubilizers, whereas higher dosage formulations require higher concentration ranges." (column 8, lines 47-60).

Therefore, a normal dosage is (0.25 x 50,000,000 IU)/ml, or 12,500,000 IU/ml (i.e. 12.5 MIU/ml). Similarly, a low dosage calculates out to be 3.125 MIU/ml. Both of these dosages of Hershenson et al. fall squarely into the claimed dosage range of claim 1 of the present invention of "about 0.6 to 24 MIU/ml of interferon-beta." Therefore, given Hershenson's indication that a normal dosage of

IFN-β in a stabilized formulation would be 12.5 MIU/ml and that both Hanisch et al. and Hershenson et al. disclose IFN-β-stabilized formulations to be used for the same purpose, there is substantial evidence to conclude that one of ordinary skill in the art, in making the Hanisch et al. formulation to be used as, for example, an antiviral agent, would consider employing a "normal" dosage quantity of IFN-β as defined by Hershenson et al. Since the combination of using the "normal" dosage of IFN-β, as taught by Hershenson et al., in the formulation of Hanisch et al., would lead one to the claimed invention, a prima facia case of obviousness for the claimed invention over Hanisch et al. in view of Hershenson et al. has been established. Furthermore, Hershenson et al. also teach process steps for the preparation of these pharmaceutical compositions (column 10, line 28 – column 16, line 41) and a container to store this composition (column 8, lines 47-60). Though neither Hanisch et al. nor Hershenson et al. teach that the containers of their invention are hermetically sealed (i.e. under sterile conditions), it would have been obvious to the artisan to use these conditions since the formulations in these containers were to be used for pharmaceutical use and sterility is a requirement for pharmaceutical compositions.

B. Claims 4 and 6 are rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. in view of Hershenson et al. The claims recite a pharmaceutical formulation comprising between 0.6 and 1 MIU/ml IFN in a 0.01 M buffer. Hershenson et al. teach that it is desirable to employ a buffer at a pH between 2 and 4, preferably at a concentration of 10 to 25 mM, to prepare stable formulations of IFN-beta (column 9, lines 13-20).

The teachings of Hanisch et al. and Hershenson et al. are recited in the above rejection under 35 USC 103. Though neither Hanisch et al. nor Hershenson et al. teach a pharmaceutical formulation comprising between 0.6 and 1 MIU/ml IFN, Hanisch et al. do teach that a preferable therapeutic amount of IFN is 0.05 mg/ml. (column 6, lines 45-51). Using the above formula, this would calculate out to 1.25 MIU/ml. This would round-off to 1 MIU/ml IFN since this is only an issue of a single digit, which is squarely in the range of 0.6 – 1 MIU/ml.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have prepared a formulation of INF-beta as described generally by Hanisch, employing a buffer of a concentration of 0.01 M as taught by Hershenson et al. because Hershensom et al. teach that "the buffer selected to maintain the formulations at the above-described pH ranges is at a concentration from about 1 to about 50 mM, more preferably from about 10 to about 25 mM. Preferably, the buffers for the pharmaceutical compositions of this invention are selected from the group consisting of phosphoric acid,

glycine and citric acid, and more preferably, the buffer is phosphate (column 9, lines 13-20)." Therefore, Hershenson teaches INF-beta in such a buffer (10 mM = 0.01 M) and that such a buffer is suitable for preparing stable pharmaceutical formulations of the IFN. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that 0.01 mM buffers described by Hershenson would be especially suitable for use in the formulation described by Hanisch. The claimed invention would have been *prima facia* obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

C. Claim 5 is rejected under 35 USC 103(a) as being unpatentable over Hanisch et al. in view of Hershenson et al. (U.S. Patent No. 5,004,605) as applied to claims 1, 3, 7, 9 and 10 above, and further in view of Cymbalista et al. (Patent No. 4,647,454). Claim 5 recites the specific buffer, acetate. Hanisch et al. teach the use of acetate buffer to dilute an HPLC pool (column 25, lines 41-46, but neither Hanisch et al. nor Hershenson et al. teach the use of acetate buffer in pharmaceutical compositions. However, Cymbalista et al. teach that acetate buffer at a pH of 3.5 is suitable for making stable formulations of IFN-beta (column 1, lines 47-56).

It would have been obvious to one of ordinary skill in the art at the time of the invention was made to have prepared a formulation of INF-beta as generally described by Hanisch et al. employing a pH 3.5 acetate buffer as described by Cymbalista because Cymbalista teaches that INF-beta is stable in acetate buffer at pH 3.5 and that such buffer is suitable for preparing stable pharmaceutical formulations of INF-beta. The ordinarily skilled artisan would have realized, in view of the teachings of the references considered collectively, that the acetate buffer described by Cymbalista would be especially suitable for use in the formulation described by Hanisch because of its appropriate pKa. The claimed invention would have been prima facia obvious as a whole at the time it was made, especially in absence of evidence to the contrary.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
September 20, 2002

Gary L. Kunz

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